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## **Liver resections can be performed safely without Pringle maneuver: A prospective study**

Maurer, Christoph A ; Walensi, Mikolaj ; Käser, Samuel A ; Künzli, Beat M ; Lötscher, René ; Zuse, Anne

**Abstract:** AIM: To evaluate liver resections without Pringle maneuver, i.e., clamping of the portal triad. **METHODS:** Between 9/2002 and 7/2013, 175 consecutive liver resections (n = 101 major anatomical and n = 74 large atypical > 5 cm) without Pringle maneuver were performed in 127 patients (143 surgeries). Accompanying, 37 wedge resections (specimens < 5 cm) and 43 radiofrequency ablations were performed. Preoperative volumetric calculation of the liver remnant preceded all anatomical resections. The liver parenchyma was dissected by water-jet. The median central venous pressure was 4 mmHg (range: 5-14). Data was collected prospectively. **RESULTS:** The median age of patients was 60 years (range: 16-85). Preoperative chemotherapy was used in 70 cases (49.0%). Liver cirrhosis was present in 6.3%, and liver steatosis of 10% in 28.0%. Blood loss was median 400 mL (range 50-5000 mL). Perioperative blood transfusions were given in 22/143 procedures (15%). The median weight of anatomically resected liver specimens was 525 g (range: 51-1850 g). One patient died postoperatively. Biliary leakages (n = 5) were treated conservatively. Temporary liver failure occurred in two patients. **CONCLUSION:** Major liver resections without Pringle maneuver are feasible and safe. The avoidance of liver inflow clamping might reduce liver damage and failure, and shorten the hospital stay.

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## Prospective Study

# Liver resections can be performed safely without Pringle maneuver: A prospective study

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**Author contributions:** Maurer CA made the conception and design of the study; Maurer CA, Walensi M, Käser SA, Künzli BM and Löttscher R acquired the data; Maurer CA, Künzli BM and Zuse A analyzed the data; Maurer CA, Walensi M, Käser SA, Künzli BM, Löttscher R and Zuse A did the interpretation of the data; Maurer CA, Künzli BM and Zuse A drafted the manuscript; Maurer CA, Walensi M, Käser SA, Künzli BM, Löttscher R and Zuse A revised and approved the final version of the manuscript.

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## Abstract

### AIM

To evaluate liver resections without Pringle maneuver, *i.e.*, clamping of the portal triad.

### METHODS

Between 9/2002 and 7/2013, 175 consecutive liver resections ( $n = 101$  major anatomical and  $n = 74$  large atypical  $> 5$  cm) without Pringle maneuver were performed in 127 patients (143 surgeries). Accompanying, 37 wedge resections (specimens  $< 5$  cm) and 43 radiofrequency ablations were performed. Preoperative volumetric calculation of the liver remnant preceded all anatomical resections. The liver parenchyma was dissected by water-jet. The median central venous pressure was 4 mmHg (range: 5-14). Data was collected prospectively.

### RESULTS

The median age of patients was 60 years (range: 16-85). Preoperative chemotherapy was used in 70 cases (49.0%). Liver cirrhosis was present in 6.3%, and liver steatosis of  $\geq 10\%$  in 28.0%. Blood loss was median 400 mL (range 50-5000 mL). Perioperative blood transfusions were given in 22/143 procedures (15%). The median weight of anatomically resected liver specimens

was 525 g (range: 51-1850 g). One patient died post-operatively. Biliary leakages ( $n = 5$ ) were treated conservatively. Temporary liver failure occurred in two patients.

### CONCLUSION

Major liver resections without Pringle maneuver are feasible and safe. The avoidance of liver inflow clamping might reduce liver damage and failure, and shorten the hospital stay.

**Key words:** Liver resection; Pringle maneuver; Blood loss

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**Core tip:** This retrospective cohort study on 175 consecutive liver resections ( $n = 101$  major anatomical and  $n = 74$  large atypical  $> 5$  cm) shows that major liver resections without Pringle maneuver are feasible and safe. The avoidance of liver inflow clamping might reduce liver damage and failure, and shorten the hospital stay.

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## INTRODUCTION

Massive haemorrhage is a key factor associated with poorer prognosis and outcome of patients undergoing liver resection<sup>[1,2]</sup>. The amount of blood loss correlates with postoperative morbidity and mortality<sup>[3]</sup>. Moreover, blood transfusion is linked to a decrease in cancer free survival<sup>[4]</sup>. Hence, it is a major goal to minimize the blood loss during liver resection. There are three main phases during liver resections when bleeding may occur: The liver mobilisation phase, the parenchymal dissection phase and the revascularization phase<sup>[1]</sup>. Portal triad clamping (PTC), also known as Pringle maneuver<sup>[5]</sup>, is the most widely used technique to reduce bleeding during the parenchymal dissection phase. In addition, vascular clamping can also be applied to control venous backflow<sup>[6,7]</sup>. Thus, total hepatic vascular exclusion can be achieved when combining PTC with clamping of the liver veins or the inferior vena cava cranial and caudad of the liver<sup>[8]</sup>. Further techniques to minimize intraoperative blood loss such as hypoventilation<sup>[9]</sup> and reduction of the central venous pressure (CVP)<sup>[10]</sup> have been developed over the last decades.

Although partial or complete vascular clamping results in reduction of blood loss, there are concerns regarding ischemia/reperfusion (I/R) injury to the liver remnant mediated by cytokines and reactive oxygen species<sup>[11,12]</sup>. Therefore, various attempts have been made to decrease

the I/R-injury associated with prolonged clamping of liver vessels: Use of drugs<sup>[13]</sup>, *in situ* cooling<sup>[14]</sup>, intermittent clamping<sup>[15,16]</sup>, ischemic preconditioning<sup>[17]</sup> and ischemic postconditioning<sup>[18]</sup>. Ischemic preconditioning involves I/R for a short period of time before exposure to prolonged I/R. The molecule nitric oxide plays a critical role in the early<sup>[11,12]</sup> and late phases<sup>[11]</sup> of ischemic preconditioning. Furthermore, during I/R-injury neutrophil and kupffer cell-induced oxidative stress, hepatic circular disturbance as well as inflammatory processes occur. Circular dysfunction is based on sinusoidal endothelial damage<sup>[19]</sup> as well as unbalance of vasoconstrictive and vasodilating transmitters such as endothelin<sup>[20]</sup>, tumor necrosis factor  $\alpha$ <sup>[21]</sup>, and interleukins<sup>[22]</sup>. Other mediators and pathways, *e.g.*, CD39 and purinergic signalling, are believed to play a role in hepatic ischemia and reperfusion injury<sup>[23]</sup>.

Thus, the molecular hepatic system is far better understood today and recent advances in surgical strategies and perioperative care have made liver resections much safer, allowing low mortality and morbidity in experienced hands. However, the question remains whether the risk of resective liver surgery can be further reduced by complete avoidance of any vascular clamping of the liver remnant and hence by minimizing the I/R injury.

The purpose of this retrospective single center data analysis was to assess the feasibility and safety of major liver resections without any Pringle maneuver or its variations. In the second step, we were interested in any differences in outcome between three subgroups: Anatomical resections, atypical resections and the combination of both, *i.e.*, the combination of anatomical and atypical resection.

## MATERIALS AND METHODS

### Study population

From September 2002 through July 2013, a prospective database was established including 175 liver resections [anatomical resections ( $n = 101$ ) and large atypical resections (specimens  $> 5$  cm in at least one diameter,  $n = 74$ )] which were performed at the occasion of 143 consecutive liver surgeries. Twenty-five patients had two stage procedures, 2 patients had 3 or more staged liver resections. The indications for these 143 liver surgeries were liver metastases ( $n = 91$ , from the following primaries: 73 colorectal cancer, 2 ovarian, 5 breast, 1 gallbladder, 1 esophageal, 1 stomach, 1 leiomyosarcoma, 1 melanoma, 2 gastrointestinal stroma tumor, and 4 with unknown primary), hepatocellular carcinoma ( $n = 11$ ), follicular nodular hyperplasia ( $n = 4$ ), liver hemangioma ( $n = 9$ ), carcinoma of the gallbladder ( $n = 4$ ), cholangiolar carcinomas ( $n = 8$ ), liver adenomas ( $n = 4$ ), hepatolithiasis ( $n = 4$ ), echinococcal cysts ( $n = 5$ ), benign liver cysts ( $n = 2$ ) and one sclerotic steatohepatitis. Patients' characteristics were summarized in Table 1. The extent of hepatectomy was depending on tumor size and localization, severity of liver steatosis and cirrhosis, age, nutritional status, preoperatively determined liver function and preopera-

**Table 1** Patients' characteristics shown as total and as subgroups according to the types of resection *n* (%)

Patient characteristics	Total	Anatomical resections	Atypical resections > 5 cm	Combination of ana-tomical and atypical resections > 5 cm	P-values <sup>3</sup>
No. of liver resections	175	84	54	37	n.d.
No. of liver surgeries	143	77	50	16	n.d.
No. of surgeries with ≥ 2 similar resections	14 (9.8)	7 (9.1)	4 (8.0)	3 (18.8)	n.d.
No. of surgeries with ≥ 1 additional wedge resection <sup>5</sup>	29 (20.3)	10 (13.0)	14 (28)	5 (31.3)	n.d.
No. of surgeries with ≥ 1 additional radiofrequency ablation	25 (17.5)	7 (9.1)	11 (22)	7 (43.8)	n.d.
Demographics					
Gender (female/male) <sup>1</sup>	74/69	41/36	24/26	9/7	0.4804 <sup>3</sup>
BMI (kg/m <sup>2</sup> ) <sup>2</sup>	25.5 (17.4-53.2)	24.8 (17.4-53.2)	27.1 (18.1-36.0)	25.2 (18.8-29.6)	0.3660 <sup>4</sup>
Age (yr) <sup>2</sup>	60.0 (16-85)	59.0 (16-85)	61.5 (28-84)	63.5 (22-78)	0.4952 <sup>4</sup>
Preoperative ASA scores 1/2/3/4 <sup>1</sup>	8/77/58/0	3/42/32/0	2/28/20/0	3/7/6/0	0.4247 <sup>3</sup>
	5/54/41/0	4/54/42/0	4/56/40.0/0	19/44/37/0	
Indications for liver surgery					< 0.0001 <sup>3</sup>
Malignant primary liver tumors	23 (16.1)	15 (19.5)	8 (16.0)	0	
Liver metastases	91 (63.6)	44 (57.1)	34 (68.0)	13 (81.2)	
Benign liver tumors	19 (13.3)	10 (13.0)	6 (12.0)	3 (18.8)	
Others	10 (7.0)	8 (10.4)	2 (4.0)	0	
Preoperative chemotherapy <sup>1</sup>	70 (49.0)	33 (42.9)	26 (52)	11 (68.8)	0.4281 <sup>3</sup>
Steatosis grade of normal liver <sup>2</sup>					0.9195 <sup>3</sup>
Steatosis 0%-9% (grade 0)	103 (72.0)	56 (72.7)	37 (74.0)	10 (62.5)	
Steatosis 10%-29% (grade 1)	26 (18.2)	14 (18.2)	8 (16.0)	4 (25.0)	
Steatosis ≥ 30% (grade 2)	14 (9.8)	7 (9.1)	5 (10.0)	2 (12.5)	
Cirrhosis (Child-Pugh A) <sup>1</sup>	9 (6.3)	5 (6.5)	4 (8.0)	0	0.8568 <sup>3</sup>

<sup>1</sup>Values are total number of patients (%); <sup>2</sup>Continuous variables are expressed as median (range); <sup>3</sup>P-values of categorical variables; <sup>4</sup>Calculated by  $\chi^2$  test and continuous ones by One-way Anova analysis of variance. No significance between the group of anatomical, atypical, and combined resections for selected variables was found, except for indications for surgery; <sup>5</sup>Liver wedge resection is defined as obtaining a liver specimen with a maximum diameter of less than 5 cm. n.d.: Not determined; BMI: Body mass index.

**Table 2** Extent of anatomical resections based on segmental and sectorial anatomy of the liver according to Brisbane classification

Type of anatomical liver resection	<i>n</i>
Extended right hemihepatectomy	6
Extended left hemihepatectomy	3
Right hemihepatectomy	31
Left hemihepatectomy	12
Right posterior sectorectomy	4
Right anterior sectorectomy	1
Left lateral sectionectomy	19
Segmentectomy	19
Bisegmentectomy	24
Trisegmentectomy	2
Total of anatomical liver resections	121

tive chemotherapy. The various extents of anatomical resections were classified according to Brisbane nomenclature<sup>[24]</sup> and were shown in Table 2.

### Intraoperative anesthesia management

Surgery was generally performed under low central venous pressure (LCVP). Therefore, the patient's internal jugular vein was cannulated using a dual-channel catheter and CVP was continuously measured. Values below 5 mmHg were targeted by limiting the volume of crystalloid infusion (lactated Ringer) and stimulating diuresis with furosemide (10-20 mg *i.v.*). At the same time, mean arterial blood pressure, determined within the radial artery, was maintained above 60 mmHg by intravenous

infusion of norepinephrine (0-10 µg/min). During dissection of liver parenchyma intermittent positive pressure ventilation was reduced to an end-expiratory level of zero mmHg to further minimize the CVP.

### Surgical procedures

Following an intravenous antibiotic single shot prophylaxis, either a roof-top or midline abdominal incision without thoracotomy was used in all patients. After exclusion of extrahepatic intraabdominal tumor spread by exploration of the abdominal cavity and the hepatoduodenal ligament, careful visual and bimanual examination of the liver was performed. At least partial mobilization of the liver including dissection of round and falciforme ligament was done in almost all procedures. Inferior hepatic veins were dissected for hemihepatectomies and/or segment 1 resections, and as necessary in other types of resection. Intraoperative ultrasonography of the liver was systematically done to accurately determine the number and location of liver tumors and their relation to hepatic blood vessels and bile ducts. A Tru-Cut<sup>®</sup>-needle (CareFusion Temno needle 14G, 11 cm, distributed by Admedics, Zuchwil, Switzerland) biopsy of grossly normal liver was sent to frozen section to assess the grades of steatosis and cirrhosis.

Blood vessels of the liver were clamped and dissected from the later liver specimen, only. Temporary or intermittent clamping of vascular structures of the liver remnant or of the liver hilum has been strictly avoided in all patients. And, neither ischemic preconditioning nor

ischemic postconditioning has been used in any of the patients. Only twice, an anterior approach according to Launois<sup>[25]</sup> was necessary due to a large tumor mass of the right liver lobe.

In all surgeries, the liver parenchyma was cut by means of water-jet dissection. The hence visualized intrahepatic blood vessels and bile ducts were dissected between ligatures or metal clips, small ones were electro-coagulated. The resection surface was treated punctually by argon plasma coagulation and checked for small bile leaks using white gauzes. The resection surface was then covered by the fibrin-based hemostyptic Tachosil® or Beriplast® (Takeda/Nycomed, Basel, Switzerland). In all patients a silicone drain (EasyFlow®, Teleflex Medical GmbH, Kernen, Germany) without suction was inserted.

### Perioperative assessment of liver function

The liver function was assessed by measurement of indocyanine green (ICG) clearance<sup>[26]</sup>. The dye ICG is metabolized and eliminated by the liver, only. Therefore, their elimination velocity is directly corresponding with the functional capacity of the liver. Plasma disappearance rate (range of normal values from 18%-25%) of ICG and the residual ICG after 15 min (R15, normal range between 0%-10%) were examined pre-, intra- and post-operatively. At the beginning of the series, 6 patients had measurement of galactose elimination capacity (GEC) instead of ICG-clearance. No intra- or postoperative controls of GEC were performed at that time. Additionally, various serum parameters were measured repeatedly, most of them daily.

The volumina of total functional liver and the anticipated functional liver remnant (FLR) were calculated by computed tomography (CT), when a resection volume of more than 40% of the total functional liver volume was anticipated. Twenty percent to 25% of total functional liver volume was regarded as a sufficient FLR in an otherwise healthy and non-steatotic liver, and 30%-40% in a steatotic or chemotherapeutically pretreated liver, respectively. In advance of 8 anatomical liver resections, induction of an atrophy-hypertrophy complex by embolization or ligation of right or left portal vein was regarded necessary. One patient underwent preoperative chemoembolization. Patients with liver cirrhosis Child-Pugh stage B were not considered candidates for surgery, and stage A patients ( $n = 9$ ) had  $\leq 2$  liver segments resected.

### Outcome measures and perioperative management

Intraoperative blood loss was calculated by adding the blood volume in the suction device plus the blood kept in towels. The indications for blood transfusion were determined individually, according to patients' preoperative heart status and haemoglobin. Generally, patients with ASA-scores 1 or 2 did not receive blood transfusions before the haemoglobin decreased below a value of 80 g/L. For patients with coronary heart disease or hemodynamic instability, the administration of blood

transfusion was less restrictive. Blood transfusions referred to the total time of hospital stay.

Postoperatively, patients were closely monitored at the intensive care unit (ICU). The Simplified Acute Physiology Score (SAPS) II was used to assess the severity of illness in intensive care patients<sup>[27]</sup>. The SAPS II predicts the risk of hospital mortality and provides an reliable estimation of the risk of death<sup>[27]</sup>.

Bilirubin content was measured from the silicon drainage tube at days 2 and 4, or daily when the drained fluid was suspicious for bile leak. Bile leakage was defined as suggested by Koch *et al.*<sup>[28]</sup> as bilirubin concentration in the drain fluid at least 3 times the serum bilirubin concentration on or after postoperative day 3; or further as the need for radiologic or operative intervention resulting from biliary collections or biliary peritonitis<sup>[28]</sup>.

Resected specimens were weighed immediately after removal. Specimens of malignant neoplasias were sent to the department of pathology for marking the resection margins with ink before formaline fixation.

Liver cirrhosis was defined as F4 fibrosis according to the METAVIR score<sup>[29]</sup>.

### Statistical analysis

Data in this study are presented as median and range or as mean  $\pm$  standard error of mean. Statistical analysis of data was performed using the GraphPad PRISM6 software (GraphPad Software Inc., San Diego, CA, United States). Comparisons of continuous variables between groups were analyzed using one-way ANOVA analysis for multiple comparisons. Categorical variables were compared by chi-square test ( $\chi^2$  test). Values of  $P < 0.05$  are considered statistically significant.

## RESULTS

Data related to the operative procedure such as operation time, CVP, blood loss and substitution, length of ICU stay, SAPS, and specimen weight is summarized in Table 3. Data are presented as total of the  $n = 143$  liver surgeries and as subgroups according to the types of resection. From the 22 patients needing perioperative blood transfusions, 7 received them intraoperatively, 1 preoperatively and 14 postoperatively.

In patients with provided preoperative volumetry of the liver, *i.e.*, patients with anticipated minimum resected volume of  $\geq 40\%$  of total functional liver volume, the median effectively resected functional volume was 53% (20%-76%). A R0-resection at the liver site could be achieved in 98/114 (86.0%) procedures for malignant liver disease. No local R2-resection did occur.

### Laboratory results

Perioperative increases or decreases of relevant laboratory parameters are shown in Table 4, as total and as subgroups according to the types of resection. Table 5 summarizes the ICG-measurements preoperatively, intraoperatively immediately upon removal of the speci-



**Table 3** Perioperative parameters and characteristics of hepatic resections, shown as total and as subgroups according to the types of resection

Perioperative data	Total (n = 143)	Anatomical resections (n = 77)	Atypical resections > 5 cm (n = 50)	Combination of anatomical and atypical resections (n = 16)	P-values
<b>Intraoperative parameters</b>					
Median operation time (min)	361 (78-726)	386 (134-726)	299 (78-692)	362 (120-567)	0.0061 <sup>3</sup>
Median CVP <sub>min</sub> during liver resection (mmHg)	4 (-5 to 14)	3 (-5 to 12)	5 (-3 to 14)	4 (-4 to 12)	0.0511
Median total blood loss per procedure (n = 143) (mL)	500 (50-5000)	500 (50-5000)	400 (50-1500)	700 (150-2400)	0.0214 <sup>3</sup>
No. of patients needing ECs (% of n = 143 procedures) <sup>1</sup>	22 (15%)	14 (18%)	6 (12%)	2 (13%)	0.9854
Mean number of ECU during total hospital stay, per procedure (n = 143) <sup>2</sup>	0.4 ± 0.1	0.5 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.4844
<b>Postoperative parameters</b>					
Median length of ICU stay (d)	3 (0-44)	3 (0-15)	3 (0-44)	3 (2-5)	0.2960
Median length of hospital stay (d)	13 (3-99)	14 (3-95)	12 (4-99)	12 (7-32)	0.0450 <sup>3</sup>
Maximum SAPS, median (range)	27 (7-40)	26 (14-40)	27 (7-40)	27 (14-39)	0.6001
Median weight of resected liver tissue (g) per procedure (n = 143)	340 (8-1850)	525 (51-1850)	53 (8-490)	352 (40-1018)	< 0.0001 <sup>3</sup>

<sup>1</sup>Since some patients had simultaneously more than 1 resection, the percentage of the perioperative need for ECs is calculated per number of procedures. P-values were calculated, comparing the variable of interest in between the different resection groups (Anova one-way analysis Kruskal-Wallis);

<sup>2</sup>Continuous variables are expressed as median (range), except presented as mean ± SEM; <sup>3</sup>Denote statistical significance among resections in the group of anatomical, atypical, and combined resections. CVP: Central venous pressure; EC: Erythrocyte concentrate; ECU: Erythrocyte concentrate unit; ICU: Intensive care unit; SAPS: Simplified acute physiology score.

mens and on postoperative day 2, again as total and as subgroups according to the type of resection. All 6 patients with preoperatively measured GEC showed values within the normal range. From further 22 patients, only the preoperative ICG-testing was available and resulted as normal (data not shown).

### Morbidity and mortality

There was one death in our series due to a preoperatively unknown high-grade stenosis at the origin of the superior mesenteric artery with consecutive extended mesenteric infarction in the postoperative course. Hence, in-hospital mortality was 1/143 procedures (0.7%).

The following major procedure-specific complications (9/143 procedures, 6.3%) occurred: 1 hemorrhage on postoperative day 9 after right hemihepatectomy in a patient needing therapeutic dosages of heparin, 5 biliary leakages treated conservatively and 2 temporary liver failures. From the later, one occurred in a patient after right hemihepatectomy who suffered from ischemic colon perforation, fecal peritonitis and multiorgan dysfunction. Another patient with extended left hemihepatectomy including segment 1 and includes hepatic artery and bile duct reconstruction for a Klatskin tumor developed intercurrent portal vein thrombosis with prolonged hepatic insufficiency. Relief was achieved by insertion of a portal stent. Finally, 1 patient with right hemihepatectomy developed postoperative peritonitis from an accidental small bowel leak, needing reintervention and laparostomy. No hepato-renal syndrome did occur.

Overall, the following advanced grades of complications according Dindo *et al.*<sup>[30]</sup> were encountered: 2 patients with grade IIIA, 4 with grade IVB and 1 with grade V complication.

## DISCUSSION

During hepatectomy, portal triad clamping developed by Pringle<sup>[5]</sup> is still commonly applied today as a routine procedure and gold standard to limit haemorrhage worldwide<sup>[18,31-35]</sup>. Clamping of the hepatoduodenal ligament and hence control of the hepatic vascular inflow is thought to reduce blood loss and to avoid blood transfusions<sup>[5]</sup>, both associated with increased perioperative morbidity and mortality<sup>[4,36,37]</sup> as well as impaired long-term outcome<sup>[34]</sup>.

Albeit the huge importance of this topic, only few studies investigated the value of Pringle maneuver in the past. No randomized study using a standard Pringle maneuver could be found in literature. And to our knowledge, only three randomized trials comparing liver resections with or without intermittent Pringle maneuver were performed so far<sup>[38-40]</sup>. The value of the intermittent Pringle maneuver is even more questionable, since these studies report conflicting results. Therefore, a very recent paper from Hoekstra *et al.*<sup>[6]</sup> was entitled "vascular occlusion or not during liver resection: The continuing story".

### Feasibility and safety of liver resections without Pringle maneuver

In the present paper, a consecutive series of major liver resections is reported without any Pringle maneuver during the total operation time in all procedures. Accordingly, a conversion to Pringle maneuver as a salvage clamping was necessary in none of the patients. Furthermore, only a minor number of patients needed perioperative blood transfusions and in-hospital-mortality was minimal with 0.7%. Hence, the feasibility and safety

**Table 4** Perioperative alterations of laboratory parameters, shown as total and as subgroups according to the types of resection

Serum parameters	Total (n = 143)	Anatomical resections (n = 77)	Atypical resections > 5 cm (n = 50)	Combination of ana-tomical and atypical resections > 5 cm (n = 16)	P-values
	Median $\Delta$ -values <sup>1</sup> (ranges)	Median $\Delta$ -values <sup>1</sup> (ranges)	Median $\Delta$ -values <sup>1</sup> (ranges)	Median $\Delta$ -values <sup>1</sup> (ranges)	
ASAT (U/L, norm < 41)	304 (-486 to 9885)	346 (-486 to 9885)	285 (-137 to 2361)	463 (-5 to 1270)	0.1747
ALAT (U/L, norm < 41)	299 (-356 to 3909)	300 (-356 to 3909)	245 (-250 to 2200)	421 (-27 to 1093)	0.2635
Bilirubin ( $\mu$ mol/L, norm < 20)	7 (-130 to 234)	9 (-130 to 234)	4 (-36 to 152)	7 (-0.1 to 33.4)	0.4605
Ammonia ( $\mu$ mol/L, norm 12-48)	39 <sup>3</sup> (14 to 155)	41 <sup>3</sup> (14 to 155)	39 <sup>3</sup> (20 to 90)	37 <sup>3</sup> (25 to 152)	0.5026 <sup>4</sup>
Albumin (g/L, norm 35-50)	-8 (-41 to 192)	-8 (-19 to 12)	-6 (-20 to 192)	-8 (-18 to 1)	0.2262
Hemoglobin (g/L, norm 130-180)	-37 (-83 to 0)	-35 (-83 to 0)	-37 (-71 to -4)	-39 (-68 to -22)	0.4654
Prothrobine time: Quick (% , norm > 70)	-27 (-108 to 62)	-32 (-81 to -9)	-22 (-53 to 13)	-35 (-63 to -7)	0.0005 <sup>2</sup>

<sup>1</sup>Medians and ranges of  $\Delta$ -values are presented.  $\Delta$ -values are calculated by the difference between preoperative value and the maximum postoperative value or postoperative nadir. P-values were calculated, comparing the  $\Delta$ -value of each serum marker among the different resection groups (One-way Anova analysis of variance); <sup>2</sup>Denote statistical significance among resections in the group of anatomical, atypical, and combined resections; <sup>3</sup>Variable is presented as median value and range of postoperative maximum, since no preoperative values were available; <sup>4</sup>P-value was calculated, comparing postoperatively determined ammonia levels (maximum) among the different resection groups (One-way Anova analysis of variance). ASAT: Aspartate transaminase; ALAT: Alanine aminotransferase.

**Table 5** Pre-, intra- and postoperative values of Indocyanine-green-clearance testing were available in 45 liver surgeries and were presented as total as well as subgroups according to the type of liver resection

ICG data <sup>1</sup>	Total (n = 45)	Anatomical resections (n = 27)	Atypical resections > 5 cm (n = 13)	Combination of anatomical and atypical resections > 5 cm (n = 5)	P-values
R15 (% , norm 0-10)					
Preoperative	3.6 (0.1 to 28.4)	3.6 (0.1 to 28.4)	3.6 (0.2 to 16.3)	2.7 (0.8 to 15)	0.4573
Intraop. after resection	12.4 (0.5 to 69.8)	17.3 (0.5 to 69.8)	6.5 (0.9 to 15.3)	22.4 (1.3 to 28.8)	0.0302 <sup>3</sup>
Postoperative day 2	5.8 (0.2 to 26.7)	7.8 (0.2 to 26.7)	3.2 (0.7 to 13.4)	7.6 (0.9 to 12.1)	0.0420 <sup>3</sup>
R15 $\Delta$ <sup>2</sup>	1.8 (-8.4 to 14.1)	4.2 (-8.4 to 14.1)	-0.2 (-5.2 to 9.8)	0.5 (-0.9 to 8.4)	0.0693
PDR (% , norm 18-25)					
Preoperative	22.2 (8.4 to 48)	21.4 (8.4 to 48)	22.2 (12.1 to 40.1)	24.1 (12.0 to 31.0)	0.6772
Intraop. after resection	14.4 (2.4 to 35.3)	11.7 (2.4 to 35.3)	18.2 (12.5 to 31.2)	9.5 (8.3 to 26.0)	0.0047 <sup>3</sup>
Postoperative day 2	19.0 (8.8 to 40.3)	17.5 (8.8 to 40.3)	22.5 (13.4 to 28.4)	17.5 (14.1 to 31.3)	0.5732
PDR $\Delta$ <sup>2</sup>	-1.4 (-15 to 37.1)	-3.7 (-12.9 to 37.1)	0.1 (-15 to 7.4)	-2.2 (-24.6 to 4.7)	0.5534

<sup>1</sup>Median values and range of data are presented. As sensitive indicator for liver function the retention rate after 15 min (R15) and the plasma disappearance rate (PDR) were evaluated; <sup>2</sup> $\Delta$  values of R15 and PDR were determined by the difference of preoperative and postoperative day 2 values. P values were calculated, comparing the variable of interest in between the different resection group (one-way Anova analysis of variance); <sup>3</sup>Denote statistical significance among resections in the group of anatomical, atypical, and combined resections. ICG: Indocyanine green clearance.

to principally avoid the Pringle maneuver seems to be demonstrated.

### Comparison of blood loss and blood transfusions without Pringle maneuver in the present series vs the literature with Pringle maneuver

In the present series, having used water jet dissection but no Pringle maneuver for all hepatic resections, the median blood loss of 500 mL was comparable with other reported series using a Pringle maneuver<sup>[38,40]</sup>, varying between 370 and 610 mL. Additionally, the percentage of patients who needed perioperative blood transfusions was 15 in this data and again comparable with data from studies having used Pringle maneuver, ranging from 13% to 36%<sup>[35,39,40]</sup>. It is noteworthy that excessive intraoperative blood losses in this series, in one patient up to 5000 mL, were exceptional and resulted all from bleeding from the inferior vena cava or the liver veins that would not have been improved by the use of a Pringle maneuver.

### Conditions facilitating the avoidance of Pringle maneuver

The following points are regarded as crucial if avoidance of Pringle maneuver is intended: Good exposure of the liver, careful planning of the dissection plane(s) on behalf of the preoperative imaging procedures and the intraoperative ultrasound, knowledge of the liver anatomy and its variants, low CVP during parenchyma dissection phase<sup>[38,41,42]</sup> and a completed learning curve in major hepatic surgery<sup>[43]</sup>. Furthermore, various dissection tools such as water jet, harmonic knife, ultrasound, humid bipolar clamp and other devices are thought to facilitate a well controlled parenchyma dissection and avoidance of major blood loss<sup>[43,44]</sup>.

### How to obtain low CVP?

The goal is a CVP below 5 mmHg at the time point of hepatic parenchyma dissection. There is a direct relation between the pressure of the hepatic sinusoidal system with CVP. Bleeding during resection phase is proportional

to the pressure gradient across vascular walls and diameter of injured vessels. Therefore, lowering of the CVP contributes to minimizing the blood loss during dissection phase<sup>[45]</sup>. Besides a close cooperation and communication between surgeon and anesthesiologist, the following measures may support lowering the CVP: Omission of any positive endexpiratory pressure during ventilation, restrictive intravenous fluid administration, forced diuresis, and a liberal use of drugs sustaining arterial blood pressure.

### **Advantages of liver resections without Pringle maneuver**

The most important advantage of abstaining from Pringle maneuver is the fact that the I/R injury to the liver remnant is almost nihil. This is especially relevant in patients with pre-existing liver damage since the toxic effects of liver ischemia with consecutive liver dysfunction lead to morbidity and mortality<sup>[15]</sup>.

Furthermore, PTC may lead to significant higher systemic vascular resistance combined with decrease in cardiac index as well as increase in mean arterial pressure and, thus, increasing risk of perioperative cardiovascular complications<sup>[16]</sup>.

Although various modifications of Pringle maneuver such as intermittent PTC, ischemic preconditioning and more recently pharmacological preconditioning have been developed to limit these disadvantages<sup>[16,46-48]</sup>, excessive bleeding during reperfusion period partially counterbalances the positive effects regarding minimizing damage of residual liver tissue.

### **Perioperative monitoring of I/R-injury and liver function**

Ischemia/reperfusion (I/R)-injury is usually monitored by measuring levels of aminotransaminases, bilirubin and prothrombin. The trauma during liver surgery caused by manipulation and parenchyma dissection usually result in a mild to moderate increase of transaminases in the serum (not more than 10-fold normal values), with a quick tendency to recover from postoperative day 1 or 2 on. Such mild increases in liver enzymes are usually not relevant for clinical outcome. However, strong elevation of transaminases (more than 20-fold normal level) with a continuous increase over at least 3 postoperative days may be the result of I/R-injury or decreased blood supply to the liver remnant. Levels of transaminases are well correlating with the ischemic damage<sup>[49]</sup>. I/R-injury may cause postoperative liver failure, mainly in preconditioned patients (*e.g.*, steatosis) with lower tolerance towards ischemia. In the present series without Pringle maneuver, no death occurred due to postoperative liver failure. Only 2 patients experienced temporary liver insufficiency, one due to a septic complication, and another due to postoperative thrombosis of portal vein. It is supposed that these favorable results with regard to postoperative liver failure may be attributed to the maintenance of optimum blood supply to the liver remnant at any time and hence the avoidance of I/R-injury. Accordingly, only moderate increases of transaminases (AST and ALT) in

this series were noticed (Table 4).

Additional serum markers that are thought to have stronger validity and more sensitive indication for liver failure and prognosis are increased bilirubin and ammonia as well as decreased prothrombin levels<sup>[50]</sup>. No serious changes in these parameters were observed with the exception of the 2 mentioned patients with severe complications.

### **Comparison of anatomical vs atypical resection**

As expected, no significant difference in perioperative and laboratory parameters was observed between the group of anatomical resections vs the group of atypical resections, with two exceptions: Operation time was significantly shorter and prothrombin time was significantly less reduced in the atypically resected group when compared to the group with anatomical resections. Especially, blood loss, blood transfusions and the length of stay in the ICU were similar in both groups.

### **Limitations of the study**

Data of this study originates from a single center. However, it is a consecutive series with prospective data recording. Large atypical liver resections were also included in this study although they would not belong to major liver resections per definition. However, with view on the study aim, we considered the inclusion of atypical liver resections of at least 5 cm diameter as appropriate, since atypical resections may be accompanied by technical difficulties and inadvertent blood loss similar to segment oriented liver resections.

In conclusion, the data of this study suggests that major liver resections may be performed safely without Pringle maneuver. The low morbidity and mortality rate might be due to minimizing the postoperative liver failure rate by avoidance of the I/R injury to the liver. Anatomical and large atypical liver resections may attempted to be performed without portal triad clamping.

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## **COMMENTS**

### **Background**

The role of Pringle maneuver in liver resection is under debate.

### **Research frontiers**

Different techniques of Pringle maneuver have been compared.

### **Innovations and breakthroughs**

The present study shows that major liver resections may be performed safely without Pringle maneuver.

### **Applications**

Major liver resections can be done avoiding Pringle maneuver.



## Peer-review

This study suggests that major liver resections may be performed safely without Pringle maneuver.

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